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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/444,284	11/19/99	VOGELS R	4231US

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ALLEN C TURNER
TRASK BRITT & ROSSA
P O BOX 2550
SALT LAKE CITY UT 84110

EXAMINER	
CHEN,S	
ART UNIT	**PAPER NUMBER**
1633	11

DATE MAILED: 09/28/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/444,284	VOGELS ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 July 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-14,16-21,24-26,28-32 and 37-58* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-14,16-21,24-26,28-32 and 37-58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicants' amendment filed 7-16-01 has been entered. Claims 1, 2, 7, 10-14, 19, 20, 24-26, 37, 41 and 42 have been amended. Claims 15 and 27 have been canceled. Claims 44-58 have been added. Claims 1, 2, 4-14, 16-21, 24-26, 28-32 and 37-58 are pending and under consideration.

Claim Objections

1. Claims 28-32 are objected to because of the following informalities: There is no article "A" in front of the term "Construct". Appropriate correction is required.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 2, 19, 20, 24-26, 37-40, 42 and 44-58 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "significantly" in claims 2, 25 and 37 is vague and renders the claims indefinite. It is unclear to what extent is considered "significantly". The specification fails to define the

term "significantly". Claims 38-40 and 42 depend on claim 2 but fail to clarify the indefiniteness.

The term "means" in claim 19 is vague and renders the claim indefinite. It is unclear as to the metes and bounds of what would be considered "means". The specification fails to define the term "means". Claim 20 depends on claim 19 and fails to clarify the indefiniteness.

The phrase "originate from" in claim 20 and the phrase "originating from" in claim 52 are vague and render the claims indefinite. It is unclear as to the metes and bounds of what would be considered "originate from" or "originating from". The phrases set forth above encompass any number of derivations such that it is unclear as to what applicants intend to claim. The specification fails to specifically define the phrases set forth above.

The term "derived" in claims 24-26, 47, 49 and 58 is vague and renders the claims indefinite. It is unclear as to the metes and bounds of what would be considered "derived". The term "derived" encompasses any number of derivations such that it is unclear as to what applicants intend to claim. The specification fails to specifically define the term "derived".

The term "increased" in claims 44 and 58 is vague and renders the claims indefinite. It is unclear as to what extent is considered "increased" and what is compared to determine whether the tropism is "increased" or not. The specification fails to specifically define the term "increased". Claims 45-57 depend on claim 44 but fail to clarify the indefiniteness.

4. Claim 37 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See M.E.P..

§ 2172.01. The omitted steps are: how to use fiber protein of adenovirus 16 in an adenovirus capsid to significantly reduce an adenovirus capsid of a tissue tropism for liver cells and whether the use of said fiber protein would significantly reduce the tissue tropism for liver cells.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1, 2, 4-14, 16-21, 24-26 and 37-58 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims read on a gene delivery vehicle comprising at least a tissue tropism for smooth muscle cells (SMC) or increased tropisom for endothelial cells, a gene delivery vehicle with a significantly reduced tropism to liver cells, or a gene delivery vehicle with tissue tropism provided by virus capsid comprising protein fragments from at least two different viruses, such as adenovirus including subgroup B (e.g. adenovirus 16) or C and non-adenovirus, a cell comprising said gene delivery vehicle, a pharmaceutical composition containing said gene delivery vehicle, and an adenovirus capsid having a tissue tropism for smooth muscle cells or significantly reduced tissue tropism for liver cells.

The specification discloses the generation of recombinant adenovirus chimeric for fiber protein of adenovirus type 11, 12, 16, 28, 35, 40 and 51 and shows that fiber chimera 12 and 28 are unable to infect HUVEC endothelial cells or smooth muscle cells, the 40L infect those cells with similar efficiency as control Ad5 virus, and adenovirus fiber 16 chimera infects HUVEC endothelial cells or smooth muscle cells significantly better than the control adenovirus type 5 (specification, bridging page 38-39, and 41). The claims encompass any unknown and unidentified gene delivery vehicle including **any adenovirus**, **any non-adenovirus**, and **any non-virus delivery vehicle** that has at least a tissue tropism for smooth muscle cells or increased tropism for endothelial cells, or with a significantly reduced tissue tropism for liver cells, and the tropism could be provided by a virus capsid comprising protein **fragments** from at least two different viruses.

The scope of the claim includes nucleic acid vectors or viruses encoding a genus of numerous structural variants of the tropism-determining protein, such as fiber protein of adenovirus, and the genus is highly variant because a significant number of structural differences between genus members is permitted. The specification fails to provide the structural features of a tropism-determining protein from different adenoviruses, non-adenoviruses, or non-virus delivery vehicles. Structural features that could distinguish compounds in the genus from others in the polypeptide class are missing from the disclosure. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed.

Since the disclosure fails to describe common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the fiber protein chimeras as disclosed in the present application is insufficient to describe the genus.

This limited information is not sufficient to reasonably convey to one skilled in the art that applicants were in possession of the claimed gene delivery vehicles. Thus, it is concluded that the written description requirement is not satisfied for the genus of proteins or the gene delivery vehicle encoding or carrying said proteins as claimed.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

With the exception of the sequences referred to above, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides, and therefore conception is not achieve regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only the nucleic acid vectors encoding the disclosed fiber protein chimeras, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

7. Claims 1, 2, 4-14, 16-21, 24-26, 28-32 and 37-58 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for adenovirus fiber 16 chimera that infects HUVEC endothelial cells or smooth muscle cells significantly better than the control adenovirus type 5 *in vitro* and none of the disclosed fiber chimeras are targeted specifically to liver and spleen *in vivo*, does not reasonably provide enablement for any gene delivery vehicle comprising at least a tissue tropism for smooth muscle cells, increased tropism for endothelial cells, or with a significantly reduced tissue tropism for liver cells for *in vitro* or *in vivo* gene delivery other than the *in vitro* use of adenoviruses encoding the disclosed fiber protein chimeras, for a cell comprising said gene delivery vehicle, a pharmaceutical composition comprising said gene delivery vehicle, a method of delivering nucleic acid to smooth muscle cells by using any adenovirus capsid *in vivo*, and a method of significantly reducing an adenovirus capsid of a tissue

tropism for a liver cells by using fiber protein of adenovirus 16 in an adenovirus capsid *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are directed to a gene delivery vehicle comprising at least a tissue tropism for smooth muscle cells or increased tropism for endothelial cells, a gene delivery vehicle with a significantly reduced tropism to liver cells, or a gene delivery vehicle with tissue tropism provided by virus capsid comprising protein fragments from at least two different viruses, such as adenovirus including subgroup B (e.g. adenovirus 16) or C and non-adenovirus, a cell comprising said gene delivery vehicle, a pharmaceutical composition containing said gene delivery vehicle, an adenovirus capsid having a tissue tropism for smooth muscle cells, increased tropism for endothelial cells, or significantly reduced tissue tropism for liver cells, a method of delivering nucleic acid to smooth muscle cells by using an adenovirus capsid *in vivo*, and a method of significantly reducing an adenovirus capsid of a tissue tropism for a liver cells by using fiber protein of adenovirus 16 in an adenovirus capsid *in vivo*.

The specification discloses the generation of recombinant adenovirus chimeric for fiber protein of adenovirus type 11, 12, 16, 28, 35, 40 and 51 and shows that fiber chimeras 12 and 28 are unable to infect HUVEC endothelial cells or smooth muscle cells, the 40L infect those cells with similar efficiency as control Ad5 virus, and adenovirus fiber 16 chimera infects HUVEC endothelial cells or smooth muscle cells significantly better than the control adenovirus type 5

(specification, bridging page 38-39, and 41). The claims encompass any unknown and unidentified gene delivery vehicle including **any adenovirus**, **any non-adenovirus**, and **any non-virus delivery vehicle** that has at least a tissue tropism for smooth muscle cells or increased tropism for endothelial cells, or with a significantly reduced tissue tropism for liver cells, and the tropism could be provided by a virus capsid comprising protein **fragments** from at least two different viruses.

The specification fails to provide adequate guidance and evidence for how to alter the tropism-determining protein of an adenovirus, a non-adenovirus, or a non-virus such that the mutated protein or chimeric protein fragments from at least two different viruses could provide tissue tropism for smooth muscle cells, increased tropism for endothelial cells or provide reduced tissue tropism for liver cells *in vitro* or *in vivo*. The claims encompass various adenoviruses, non-adenoviruses, such as retroviruses, and non-virus gene delivery vehicle derived from various organisms. "At present, six different subgroups of human adenoviruses have been proposed which in total encompass approximately 50 distinct adenovirus serotypes. Besides these human adenoviruses, many animal adenoviruses have been identified" (Specification, page 4). "These serotypes differ in at least capsid proteins (penton-base, hexon), proteins responsible for cell binding (fiber protein), and proteins involved in adenovirus replication. It is unknown to what extent the capsid proteins determine the difference in tropism found between the serotypes. It may well be that post-infection mechanisms determine cell type specificity of adenoviruses" (specification, page 5). Subgroup B1 of adenovirus includes serotype 3, 7, 16, 21 and 51, and

subgroup B2 includes 11, 14, 34 and 35. The specification of the present application states that "efficient infection of SMC is not a general trade of all subgroup B fiber molecules. Clearly fiber 16 and fiber 11 are better suited for infection of SMC than fiber 35 and fiber 51" (page 42). In view of the scope of the claimed invention that encompasses various adenoviruses, non-adenoviruses, and non-virus gene delivery vehicles, and the unpredictability of whether said adenoviruses, non-adenoviruses, and non-virus gene delivery vehicles would have a tissue tropism for SMC, increased tropism for endothelial cells, or reduced tissue tropism for liver cells *in vitro* or *in vivo*, one skilled in the art at the time of the invention would no know how to use the claimed invention.

Further, the claims encompass various altered tropism-determining proteins, chimeric proteins, and fragments of virus capsid protein. It was known in the art that the amino acid sequence of a polypeptide determines its structural and functional properties (including half-life), and predictability of which amino acid(s) can be removed from or added to a polypeptide's sequence and still result in similar activity or result in stabilization of the protein is extremely complex, and well outside the realm of routine experimentation. Rudinger, 1976 (Peptide Hormones, Parsons, University Park Press, Baltimore, p. 1-7) points out that "The significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study" (e.g. p. 6). Kaye et al., 1990 (Proc. Natl. Acad. Sci. USA, Vol. 87, pp. 6922-6926) discloses that a single amino acid substitution results in a retinoblastoma protein defective in phosphorylation

and oncoprotein binding (e.g. title). It is unclear whether an altered tropism-determining protein, chimeric protein having protein fragments from different viruses could still maintain their specific tropism to a specific cell type as compared to their wild type proteins. Therefore, it would be unpredictable whether various altered tropism-determining proteins, chimeric proteins having protein fragments from at least two different viruses, such as fragments of virus capsid proteins, could provide a tissue tropism for SMC, increased tropism for endothelial cells, or reduced tissue tropism for liver cells *in vitro* or *in vivo*.

In addition, the specification states "The invention related to the field of molecular genetics and medicine. In particular the present invention relates to the field of **gene therapy**, more in particular to **gene therapy using adenoviruses**" (specification, page 1). Therefore, the claims read on **gene therapy** *in vivo* in light of the specification of the present application. The term "pharmaceutical" in claim 21 also replies therapeutic effects *in vivo*. The specification only discloses adenovirus fiber 16 chimera infects HUVEC endothelial cells or smooth muscle cells significantly better than the control adenovirus type 5 and none of the disclosed fiber chimeras are targeted specifically to liver and spleen *in vivo*. The specification fails to provide adequate guidance and evidence for the correlation between the gene delivery vehicle encoding a protein of interest and a particular disease in a patient. The specification also fails to provide adequate guidance and evidence for how to deliver the gene delivery vehicle expressing any gene product under the control of any promoter to a patient and sufficient gene products could be produced at

the targeted site so as to provide therapeutic effects for a particular disease or disorder in said patient *in vivo*.

The nature of the invention being gene therapy, the state of the prior art was not well developed and was highly unpredictable at the time of filing. While progress has been made in recent years for gene transfer *in vivo*, vector targeting to desired tissues *in vivo* continues to be unpredictable and inefficient as supported by numerous teachings available in the art. For example, Deonarain (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69) indicate that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain reviews new techniques under experimentation in the art which show promise but states that such techniques are even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). Verma (Sept. 1997, Nature, Vol. 389, pages 239-242) reviews vectors known in the art for use in gene therapy and discusses problems associated with each type of vector. The teachings of Verma indicate a resolution to vector targeting has not been achieved in the art (see entire article). Verma also teaches appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (page 240, sentence bridging columns 2 and 3). Crystal (1995, Science, Vol. 270, page 404-410) also reviews various vectors known in the art and indicates that "among the design hurdles for all vectors are the need to increase the efficiency of gene transfer, to increase target specificity and to enable the transferred gene to be regulated" (page 409).

Eck et al., 1996 (Goodman & Gilman's The Pharmacological Basis of Therapeutics, McGraw-Hill, New York, p. 77-101) states that the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced are important factors for a successful gene therapy *in vivo* (e.g. bridging pages 81-82). In view of such, one skilled in the art at the time of the invention would not know how to make and/or use the claimed invention.

Therefore, it is concluded that based upon the nature of the claimed invention, the state of the art, the unpredictability found in the art, the teaching and working examples provided, and the breadth of the claims that it would require a skilled artisan at the time of the invention undue experimentation to practice over the full scope of the invention claimed.

8. Claims 28-32 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 28-32 recite adenovirus sequences without providing adequate sequence information regarding the genome of the adenovirus claimed. This rejection may be obviated by appropriate deposit of the nucleic acid construct claimed.

The invention consists of adenovirus constructs. Since the constructs are essential to the claimed invention, they must be obtainable by a repeatable method set forth in the specification or otherwise be readily available to the public. If the construct is not so obtainable or available, the requirements of 35 U.S.C. § 112, regarding "how to make", may be satisfied by a deposit of the constructs. The specification does not disclose a repeatable process to obtain the constructs and it is not apparent if these are readily available to the public. It is noted there is no indication in the specification as to public availability to the claimed constructs. If the deposits are made under the terms of the Budapest Treaty, then an affidavit or declaration by Applicant, or a statement by an attorney of record over his or her signature and registration number, stating that the specific construct has been deposited under the Budapest Treaty and that the construct will be irrevocably and without restriction released to the public upon the issuance of a patent, would satisfy the deposit requirement made herein.

If the deposit has not been made under the Budapest Treaty, then in order to certify that the deposit meets the criteria set forth in 37 CFR 1.801-1.809, applicants may provide assurance of compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that

(a) during the pendency of this application, access to the invention will be afforded to the Commissioner upon request;

(b) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;

(c) the deposit will be maintained in a public depository for a period of 30 years or 5 years after the last request or for the effective life of the patent, whichever is longer; and,

(d) a test of the viability of the biological material at the time of deposit (see 37 CFR 1.807); and,

(e) the deposit will be replaced if it should ever become inviable.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 1, 4, 11, 14, 16, 17, 19 and 21 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Wickham et al., 1997 (Journal of Virology, Vol. 71, No. 11, p. 8221-8229).

Claims 1, 4, 11, 14, 16, 17 and 21 are directed to a gene delivery vehicle, such as an adenoviral nucleic acid having reduced replication, comprising at least a tissue tropism for SMC

via viral capsid protein fragment, and a pharmaceutical composition comprising said gene delivery vehicle. Claim 17 specifies the gene delivery vehicle further comprises a non-adenoviral nucleic acid. Claim 19 is directed to a cell for producing a gene delivery vector having a tissue tropism for SMC via a means for the production of an adenoviral fiber protein comprising at least a tissue tropism determining fragment of a subgroup B adenoviral fiber protein.

Wickham teaches generation of two adenovirus (Ad) vectors (E1-E4+) which contain modifications to the Ad fiber coat protein that redirect virus binding to either alpha integrin (AdZF(RGD)) or heparan sulfate (AdZF(pK7)) cellular receptors. AdZF(RGD) increased gene delivery to endothelial and SMC expressing alphav integrin, and AdZF(pK7) increased transduction 5-500 fold in endothelial and SMC lacking high levels of Ad fiber receptor. Wickham also teaches producing adenoviruses containing AdZF(pK7) or AdZF(RGD) vector by using a human embryonic kidney (293) cells which contains the complementary E1 region for virus growth (e.g. p. 8222). Wickham suggests alteration of the natural tropism of adenovirus will permit gene transfer into specific cell types and greatly broaden the scope of target diseases via Ad, and demonstrates the feasibility of tissue-specific receptor targeting in cells which express low levels of Ad fiber receptor (e.g. abstract, fig. 2). Thus, claims 1, 4, 11, 14, 16, 17 and 21 are clearly anticipated by Wickham.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 1, 4-14, 17-19, 24, 26 and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wickham et al., 1997 (Journal of Virology, Vol. 71, No. 11, p. 8221-8229) in view of Stevenson et al., 1997 (Journal of Virology, Vol. 71, No. 6, p. 4782-4790) and Woo et al., 1997 (US Patent No. 5,631,236).

Claims 1, 4-14, 17, 18, 24, 26 and 43 are directed to a gene delivery vehicle, such as an adenoviral nucleic acid having reduced replication, comprising at least a tissue tropism for SMC via viral capsid protein, such as fiber protein, fragments from at least two different viruses, such as subgroup B adenovirus (e.g. adenovirus 16) or subgroup C adenovirus, an adenoviral capsid

having a tissue tropism for SMC cells wherein said capsid comprises proteins from at least two different adenoviruses including a fragment of a fiber protein from subgroup B adenovirus, and a method of delivering nucleic acid to SMC via administering to SMC an adenovirus capsid. Claim 18 specifies the gene delivery vehicle further comprises a non-adenoviral nucleic acid encoding the protein as recited in the claim. Claim 19 is directed to a cell for producing a gene delivery vector having a tissue tropism for SMC via a means for the production of an adenoviral fiber protein comprising at least a tissue tropism determining fragment of a subgroup B adenoviral fiber protein.

Wickham teaches generation of two adenovirus (Ad) vectors (E1-E4+) which contain modifications to the Ad fiber coat protein that redirect virus binding to either alphav integrin (AdZF(RGD)) or heparan sulfate (AdZF(pK7)) cellular receptors. AdZF(RGD) increased gene delivery to endothelial and SMC expressing alphav integrin, and AdZF(pK7) increased transduction 5-500 fold in endothelial and SMC lacking high levels of Ad fiber receptor. Wickham also teaches producing adenoviruses containing AdZF(pK7) or AdZF(RGD) vector by using a human embryonic kidney (293) cells which contains the complementary E1 region for virus growth (e.g. p. 8222). Wickham suggests alteration of the natural tropism of adenovirus will permit gene transfer into specific cell types and greatly broaden the scope of target diseases via Ad, and demonstrates the feasibility of tissue-specific receptor targeting in cells which express low levels of Ad fiber receptor (e.g. abstract, fig. 2).

Wickham does not teach using fiber protein from two different adenoviruses, an adenovirus encoding the protein recited in claim 18, and a method of delivering nucleic acid to SMC via administering to SMC an adenovirus capsid.

Stevenson teaches preparation of a chimeric fiber cDNA having Ad3 (subgroups B) fiber head domain fused to the Ad5 (subgroup C) fiber tail and shaft incorporated into the genome of an adenovirus vector with E1 and E3 deleted region encoding beta-galactosidase to generate Av9LacZ4, and a recombinant adenoviruses containing the chimeric fiber protein. Stevenson teaches that three cell lines (THP-1, MRC-5, and FaDu) were more efficiently transduced by the vector comprising the Ad3 fiber head than by the Ad5 fiber vector. Stevenson suggests that "exchange of fiber head domain is a viable approach to the production of adenovirus vectors with cell-type specific transduction properties" and may "extend this approach to the use of ligands for a range of different cellular receptors in order to target gene transfer to specific cell types at the level of transduction" (e.g. abstract).

Woo teaches a novel method of treating localized solid tumors and papilloma in an individual by introducing a recombinant adenoviral vector containing the HSV-Tk gene (e.g. abstract).

It would have been obvious for one of ordinary skill at the time of the invention to substitute DNA encoding the modified Ad fiber protein as taught by Wickham with the chimeric fiber cDNA having Ad3 (subgroups B) fiber head domain fused to the Ad5 (subgroup C) fiber tail and shaft as taught by Stevenson for the tropism of SMC because it was general knowledge

to substitute a DNA segment with another DNA segment in an adenoviral vector for the purpose of changing the tropism of the adenovirus and Stevenson teaches "exchange of fiber head domain is a viable approach to the production of adenovirus vectors with cell-type specific transduction properties". It also would have been obvious for one of ordinary skill at the time of the invention to deliver nucleic acid to SMC by administering to said SMC with an adenovirus capsid because of the collective teachings of Wickham and Stevenson in producing an adenovirus containing the chimeric fiber cDNA having Ad3 (subgroups B) fiber head domain fused to the Ad5 (subgroup C) fiber tail and shaft and transduction of SMC with said adenovirus, and the teaching of Woo in treating solid tumors with recombinant adenoviral vector expressing the HSV-Tk gene.

One having ordinary skill at the time the invention was made would have been motivated to do so in order to alter the natural tropism of adenovirus so as to permit gene transfer into specific cell types, such as SMC and endothelial cells, and greatly broaden the scope of target diseases via Ad as taught by Wickham, to target gene transfer to specific cell types at the level of transduction as taught by Stevenson, and to treat solid tumors by using adenoviral vector *in vivo* as taught by Woo with reasonable expectation of success.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 9 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Clark can be reached on (703) 305-4051. The fax phone number for this group is (703) 308-4242.

Questions of formal matters can be directed to the patent analyst, Kimberly Davis, whose telephone number is (703) 305-3015.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Shin-Lin Chen, Ph.D.